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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/904,532      | 07/13/2001  | Avi Ashkenazi        | 10466/50            | 2313             |

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EXAMINER

DEBERRY, REGINA M

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1647

DATE MAILED: 11/12/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/904,532

Applicant(s)

ASHKENAZI ET AL.

Examiner

Regina M. DeBerry

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 October 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 39-51 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 39-51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6,12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

***Status of Application, Amendments and/or Claims***

The information disclosure statements filed 14 March 2002 (Paper No. 6) and 15 October 2002 (Paper No. 12) were received and complies with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 26 August 2002 (Paper No. 10) has been entered in full. The amendment filed 10 October 2002 (Paper No. 11) has been entered in full. Claims 1-38 were cancelled. New claims 39-51 were added. Claims 39-51 are under examination.

***Priority***

According to the priority statement it appears that the claimed subject matter defined in the instant application is supported by US Provisional Application 60/059184 filed 9/17/97. Based on the information given by Applicant and an inspection of the parent applications, the Examiner has concluded that the subject matter defined in this application is supported by the disclosure in PCT application serial number PCT/US98/19330 filed 9/16/98 but is not supported by the US Provisional Application 60/059184 filed 9/17/97. Provisional 60/059184 does not teach how to use the instant protein and thus does not provide an enabling disclosure. Accordingly, the subject matter defined in claims 39-51 has an effective date of 9/16/98.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page number(s) of any parent application filed prior to 9/16/98 which specifically supports the

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particular claim limitation for each and every claim limitation in all of the pending claims which Applicant considers to have been in possession of and fully enabled for prior to 9/16/98.

### ***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. This occurs on pages 69, 71, 147, 154, 167 and 178. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

an isolated protein having 100% amino acid sequence identity to the polypeptide of SEQ ID NO:127 or the mature form thereof and

an isolated protein having 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO:127 or the mature form thereof, wherein the isolated polypeptide inhibits vascular endothelial growth factor (VEGF) stimulated proliferation of endothelial cell growth or induces redifferentiation of chondrocytes

does not reasonably provide enablement for:

an isolated protein **not identical to at least the mature form of SEQ ID NO:127 which does not have the instant activities**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:127, the extracellular domain thereof, or the extracellular domain thereof lacking its associated signal peptide. There is no functional limitation in the claims. Applicants have taught the polypeptide sequence of SEQ ID NO:127 (amino acids 1-282), the signal peptide sequence (amino acids 1-30 of SEQ ID NO:127), the extracellular domain (approximately amino acids 31-229) and the transmembrane domain (amino acids 230-246 of SEQ ID NO:127) (specification, Figure 46). This polypeptide was shown to inhibit vascular endothelial growth factor (VEGF) stimulated proliferation of endothelial cell growth (pages 204-205, EXAMPLE 66) and induce redifferentiation of chondrocytes (page 235, EXAMPLE 95).

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. The specification suggests that the polypeptide of SEQ ID NO:127 is a new member of the low-density lipoprotein receptor family (page 18). The functional domain of a receptor is the mature form.

There are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID NO:127 or the mature form thereof. There are two conclusive functions attributed to PRO224: inhibition of VEGF stimulated proliferation of endothelial

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cell growth (pages 204-205, EXAMPLE 66) and inducing redifferentiation of chondrocytes (page 235, EXAMPLE 95).

The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the anti-VEGF stimulated proliferation function or the induction of redifferentiation of chondrocytes function disclosed in the instant specification. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation. The specification does not provide guidance for using polypeptides related to (*i.e.*, 80%-99% identity) but not identical to at least amino acids 31-229 of SEQ ID NO:127 (extracellular domain) which do not have the single specific disclosed activity show for PRO224. Relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer *et al.* (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2).

For these reasons, which include the complexity and unpredictability of the nature of the invention in terms of the lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:127, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure

and function, the large quantity of experimentation necessary to screen same for the disclosed activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the lack of direction or guidance for using polypeptides that are not identical to at least the extracellular domain of SEQ ID NO:127, and the breadth of the claims for structure without function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence (SEQ ID NO:127). The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

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combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:127, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. PRO224 is identified as a new member of the low-density lipoprotein receptor family (page 18). The limitations, "the polypeptide...lacking its associated signal peptide" and "the extracellular domain...lacking its associated signal sequence" (claim 39, parts (b) and (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

### **Conclusion**

No claims are allowed.

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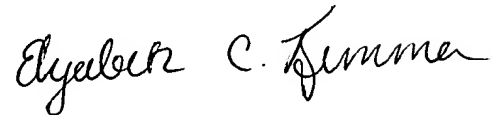
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



RMD  
November 7, 2002



ELIZABETH KEMMERER  
PRIMARY EXAMINER